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Russell L. Regnery
Centers for Disease Control and Prevention

James E. Childs
james.childs@yale.edu

Jane E. Koehler
University of CaliforniaA IDS Research Program

Infections Associated with *Bartonella* Species in Persons Infected with Human Immunodeficiency Virus

Russell L. Regnery, James E. Childs, and Jane E. Koehler

From the Viral and Rickettsial Zoonoses Branch, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; and the Division of Infectious Diseases, University of California, San Francisco, California

Two members of the genus *Bartonella*, *Bartonella quintana* (formerly *Rochalimaea quintana*) and *Bartonella henselae* (formerly *Rochalimaea henselae*), have recently been recognized as agents of severe or fatal disease in patients infected with human immunodeficiency virus (HIV). The development of infection with *B. henselae* in HIV-infected individuals has been associated with traumatic contact with cats (scratches or bites), and domestic cats have been identified as a major reservoir for this organism. Specific information regarding the transmission of *B. henselae* to humans is not yet available, but common-sense precautions that minimize exposure to cat-associated organisms are appropriate. Preliminary accounts suggest that *B. quintana* infections are more common than *B. henselae* infections among HIV-infected individuals in San Francisco. The source of infection with *B. quintana* and the mechanism of its transmission remain unknown.

The four species of the genus *Rochalimaea* (*Rochalimaea quintana, Rochalimaea henselae, Rochalimaea elizabethae,* and *Rochalimaea vinsonii*) were recently shown to be closely related to the sole member of the genus *Bartonella* (*Bartonella bacilliformis*) [1]. Because *Bartonella* was described before *Rochalimaea,* the former designation takes precedence over the latter. Thus the name *Bartonella* will be used in this document to describe all five members of the expanded genus. However, in many publications the name *Rochalimaea* may still be used. Species names remain unchanged; e.g., *R. henselae* is now known as *Bartonella henselae.*

Background

The diseases known to be associated with *Bartonella* species are listed in table 1. Historically, the best-known member of the genus is *Bartonella quintana,* the bacterium that caused trench fever in World War I [2]. In 1990, DNA sequences closely related to *B. quintana* were identified in the lesions of patients with bacillary angiomatosis (BA) [3], a vascular proliferative disorder that occurs in HIV-infected persons [4]. Independently, a fastidious gram-negative rod was isolated from HIV-infected patients with a relapsing febrile illness [5], and similar bacilli were noted in tissue from patients with an unusual hepatic disease known as peliosis hepatis [6]. A novel species, *B. henselae,* was later isolated and fully characterized [7, 8]. Gene sequences from *B. henselae* were identical to those previously identified in biopsied tissues from patients with BA and peliosis hepatis [3, 7]. The subsequent isolation of bacteria directly from cutaneous lesions of BA revealed that either *B. henselae* or *B. quintana* can cause this disease [9]. Over the past decade, since BA was first described by Stoler et al. in New York City [10], the spectrum of bartonella infection in patients with concomitant HIV infection has been expanding; now included are endocarditis [11, 12] and angiomatous lesions involving many organs, including the skin, liver, lung, spleen, bone, and brain. (For a summary of the involvement of various organs, see [13].) Although cutaneous BA can be an indolent disease with remissions and exacerbations over many months [4], its systemic symptoms can be debilitating. When bartonella infection remains undiagnosed in patients with HIV infection, it can be fatal [14].

Recently, *B. henselae* was found to be the cause of cat-scratch disease [15–17] in addition to some cases of BA. The reason for the different host responses to infection with *B. henselae* (granulomatous in the immunocompetent host and vascular proliferative in the immunocompromised host) is unknown. Immunocompetent people with *B. henselae* infection can develop a prolonged febrile and relapsing illness [18] like that seen in HIV-infected patients [5, 7].

Infection with the remaining three *Bartonella* species has not been reported in HIV-infected patients. *Bartonella elizabethae* caused severe endocarditis in one immunocompetent patient [19]. No human infections with *Bartonella vinsonii* have been identified. *B. bacilliformis,* the etiologic agent of bartonellosis, causes biphasic illness: the acute febrile phase is known as Oroya fever, and the chronic phase with cutaneous vascular lesions is known as verruga peruana [20]. These cutaneous

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Reprints or correspondence: Dr. Russell Regnery, Viral and Rickettsial Zoonoses Branch, Mailstop G-13, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, Georgia 30333.

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Table 1. Diseases with well-documented associations with *Bartonella* species.

Immune status, disease	Causative species of *Bartonella*
Competent	
Cat-scratch disease	*B. henselae*
Trench fever	*B. quintana*
Bartonellosis	*B. bacilliformis*
Endocarditis	*B. henselae, B. quintana, B. elizabethae*
Compromised	
Bacillary angiomatosis	*B. henselae, B. quintana*
Relapsing bacteremia with fever	*B. henselae, B. quintana*
Endocarditis	*B. henselae, B. quintana*

eruptions are sometimes indistinguishable from those of BA; however, infection with *B. bacilliformis* has been reported only in the Andes Mountains of South America [20].

Numerous reports in the literature describe good clinical responses of immunocompromised patients with BA or peliosis hepatis to treatment with erythromycin or doxycycline. In the experience of one of the authors (J.E.K.), erythromycin, doxycycline, tetracycline, and minocycline have been successful in the treatment of these conditions (table 2) [13]. Rifampin and gentamicin appear to have some clinical efficacy; although there is insufficient evidence to recommend the use of either agent alone, these drugs may be of value when combined with a first-line agent for the treatment of immunocompromised patients with severe *Bartonella*-associated disease (e.g., osteomyelitis, peliosis hepatis, or endocarditis). There are conflicting reports regarding the response of BA lesions in immunocompromised patients to treatment with quinolones [13].

The optimal duration of treatment for immunocompromised individuals is unknown, but patients with cutaneous BA should receive an appropriate antibiotic for at least 2 or 3 months; patients with more severe disease (osteomyelitis, peliosis hepatis) should receive a minimum of 3 or 4 months of antibiotic therapy. Most patients treated with tetracycline or erythromycin for 4 months do not have a relapse. However, like salmonellosis and various other bacterial infections, bartonella infection can relapse in some cases even after prolonged therapy with erythromycin [9]. Immunocompromised patients with bartonella infection should be followed closely if antibiotic treatment is stopped after 4 months; if a relapse occurs, these individuals should be treated indefinitely with suppressive antibiotics.

Although the clinical response to antibiotics is dramatic among immunocompromised patients with bartonella infection, the response of people with intact immune systems and cat-scratch disease or relapsing bacteremia remains equivocal [18, 21]. The curious influence of the host's immune status on apparent antibiotic efficacy may be related to different manifestations of the syndromes. Cat-scratch disease is clinically defined by swollen lymph nodes and granulomatous lesions—signs that cannot develop in severely immunocompromised hosts and that cannot be expected to regress as long as antigen is present. It is possible that persons with intact immune systems, unlike severely immunocompromised patients, sequester viable or antigenically active *Bartonella* within either cells or immune-mediated tissue complexes (e.g., granulomas).

Incidence

Preliminary estimates of the prevalence of antibody to *Bartonella* among apparently healthy humans range from 4% to 6% [15, 22]. Cat-scratch disease is clinically diagnosed in an estimated 22,000 persons each year in the United States [23]. The incidence of *Bartonella*-associated disease among HIV-infected persons is unknown. These infections may go unrecognized in the majority of cases, and the interval between infection and the diagnosis of BA can cover months or even a year [9]. In addition, disease in immunocompromised persons may represent reactivation of infection rather than primary infection: low-titer antibodies to *Bartonella* have been documented in banked sera obtained from HIV-infected people before the diagnosis of BA, with increased titers at the time of diagnosis [24].

Bartonella infections in HIV-infected people often are not recognized for a number of reasons. First, cutaneous BA lesions can be clinically indistinguishable from Kaposi's sarcoma [25]; in these cases, BA can be distinguished only by biopsy with histopathologic examination. A characteristic vascular proliferation with a mixed inflammatory infiltrate is evident upon hematoxylin and eosin staining of biopsied BA tissue, and bacillary organisms can be demonstrated by Warthin-Starry staining [4]. Second, hepatic disease caused by *Bartonella* species—even the relatively dramatic form, peliosis hepatis—can be indistinguishable from other infectious or malignant conditions that cause hypodense lesions demonstrable by abdominal CT (e.g., lymphoma, Kaposi's sarcoma, extrapulmonary pneumocystosis, and bacterial and fungal abscesses). Third, clinicians evaluating HIV-infected patients may fail to consider *Barto-*

Table 2. Clinical response of HIV-infected individuals with bacillary angiomatosis or peliosis hepatis to antibiotic treatment (San Francisco General Hospital/University of California at San Francisco, 1987–1995).

Definite	Possible	Inconclusive	None
Erythromycin	Gentamicin	Ciprofloxacin	Penicillin
Doxycycline	Rifampin	Ceftriaxone	Penicillin derivatives
Tetracycline		Trimethoprim/ sulfamethoxazole	First generation cephalosporins
Minocycline			

NOTE. Table is adapted with permission from [13].

Table 3. Manifestations of bartonella infections in HIV-infected patients.

Organ	Manifestation
Skin (bacillary angiomatosis)	Diverse presentations, including lesions resembling Kaposi's sarcoma, angiomatous nodules, friable vascular lesions, red papules, pedunculated lesions, and deep subcutaneous masses
Bone	Extremely painful osteolysis, lytic lesions on radiography (positive technetium scan)
Lymph node	Enlargement
Heart	Valvular vegetation, fever, weight loss
Blood	Fever, thrombosis
Liver/spleen bacillary peliosis	Hypodense lesions, hepatosplenomegaly on CT, elevated values in liver function tests (e.g., alkaline phosphatase), pancytopenia, thrombocytopenia
Other	Involvement of brain, gastrointestinal tract, lungs, etc.

NOTE. Table is adapted from [26].

nella in the differential diagnosis of a febrile illness in the absence of cutaneous lesions or peliosis hepatis (table 3) [26].

Finally, culture of *Bartonella* species is difficult, requiring special media and techniques. This situation compounds the problems encountered in the diagnosis of isolated bartonella bacteremia, even when this diagnosis is considered. A genus-specific IgG indirect fluorescent antibody (IFA) test recently developed at the Centers for Disease Control and Prevention (CDC) is both sensitive and specific for the confirmation of a diagnosis of cat-scratch disease [15, 22]. Patients with cat-scratch disease typically have elevated titers of *Bartonella*-specific IgG antibody at the time of their presentation to the health care practitioner; titers appear to diminish within a year of the original diagnosis [22]. The diagnosis of cat-scratch disease by IFA test has correlated well (98%; 55 of 56 cases) with clinical diagnosis and skin testing [27], and the specificity of the IFA test is ~95% [15, 22]. An IgM ELISA has also shown relatively good sensitivity (95%; 53 of 56 cases) in studies of patients with cat-scratch disease diagnosed by skin testing; however, the specificity of the ELISA was only 77% (43 of 56 cases) [27]. Preliminary results suggest that the IFA test shows promise in the laboratory confirmation of bartonella infections in HIV-infected patients [24]. Improved diagnostic tests will result in more accurate assessment of the true incidence of bartonella infection in this population and may facilitate appropriate treatment. Reagents for IFA testing for *Bartonella* are currently available to regional and state health laboratories from the CDC. Additional diagnostic techniques for the serological testing of patients (including commercial tests) are being developed. However, before their widespread use as diagnostic tools, additional blinded, side-by-side evaluations of specificity and sensitivity for the various *Bartonella*-associated syndromes are necessary.

Source of Infection and Risk Factors

Numerous anecdotal reports have described exposure to and contact with cats before the development of BA in immunocompromised patients [13]. A case-control analysis found that recent contact with cats was the only environmental risk factor associated with BA [28]. Patients with BA—but not control patients—were statistically more likely to have been licked, scratched, or bitten by a cat before developing this illness. The amount of time spent with a cat was associated with the degree of risk. As had previously been documented in studies of cat-scratch disease in HIV-uninfected populations [22, 29], ownership of kittens or young cats (i.e., those <1 year old) posed a particularly high risk to HIV-infected persons for acquiring *B. henselae*–associated disease [28].

It has recently been shown that the domestic cat provides a major reservoir from which HIV-infected patients apparently acquire *B. henselae* infection. Seven pet cats belonging to four patients with confirmed BA due to *B. henselae* had this organism isolated from the bloodstream, as did 25 (41%) of 61 randomly sampled cats in San Francisco [30]. Seroepidemiological studies indicate that *B. henselae* infection of domestic cats is also common in other regions of the United States, with a prevalence of *Bartonella*-specific antibodies ranging from 14% to 50% [22, 31]. An estimated one-third of all households in the United States include a cat [32], and cats may be persistently bacteremic for prolonged periods without obvious signs of illness [30, 33]. Thus, pet cats pose a real but probably small risk of *B. henselae* infection to HIV-infected owners [34].

Exposure to kittens with fleas has been reported to be a risk factor for cat-scratch disease. Thus, it has been suggested that arthropod vectors transmit *B. henselae* among felines and/or between felines and humans, although a cat scratch or bite has been more strongly associated with acquisition of the disease [22]. Viable *B. henselae* bacilli have been isolated from fleas from cats [30], but the fleas' ability to transmit *B. henselae* has not been established. Ticks also have been suggested as possible vectors of *B. henselae* [18, 22].

Early in the investigation of *Bartonella*-associated diseases, the human body louse (*Pediculus humanus*) was identified as a vector of human-to-human transmission of *B. quintana* [2]. However, virtually nothing is known about possible arthropod vectors or possible alternative vertebrate reservoirs of *B. quintana* infections today. *B. bacilliformis* can be transmitted by the sandfly (genus *Phlebotomus*) within its naturally occurring geographic range [20]. Neither nonhuman reservoirs nor possible arthropod vectors of *B. elizabethae* are known. Because infections with *B. bacilliformis* and *B. quintana* can be arthropod-borne, it is plausible that other members of the genus (e.g., *B. henselae*) also have arthropod vectors.

The risk of developing relatively severe disease due to *Bartonella* species appears to increase as the $CD4^+$ cell count decreases. In a recent review, the mean $CD4^+$ cell count of 15 HIV-infected patients with *Bartonella*-associated disease was $57/mm^3$ [13]. In a case-control study of 42 patients with bartonella infection, patients with BA were statistically more likely than controls to have a $CD4^+$ cell count of $<200/mm^3$ [35].

Prevention

Physicians should recognize the potential psychological value of companion animals for seriously ill persons. However, immunocompromised persons who have no prior emotional attachment to a cat and who are concerned about the risk of *B. henselae* infection should consider alternative species for companionship. Of course, the potential for zoonotic disease associated with nonfeline companion-animal species also must be considered [34].

Because data are not yet available on the degree of risk to humans for *B. henselae* infection related to contact with cats or on the mode of *B. henselae* transmission from one cat to another or from cats to humans, specific recommendations for prevention are currently limited to common-sense precautions [34, 36]. Adult cats pose a lesser risk than do cats <1 year old. Severely immunocompromised persons should avoid rough play with cats that might result in scratches or bites and should not allow a cat to lick open cuts or wounds. Contamination of broken skin with cat secretions should be avoided, and cat-associated wounds should be washed immediately with soap and water. Control of fleas is appropriate.

Recommendations regarding the prevention of *B. quintana* infection are presently limited to the avoidance of exposure to the human body louse.

Research Priorities

Bartonella-associated disease among HIV-infected persons has been described only recently, but it is already evident that treatment and preventive efforts can be beneficial. The incidence of *Bartonella*-associated disease must be established, and the spectrum of disease (including syndromes currently undiagnosed) must be more completely elucidated. Economical, rapid, sensitive, and specific methods for laboratory diagnosis need to be further developed and disseminated to local health care centers. The timing, type, and duration of antibiotic prophylaxis for initial or reactivated bartonella infection in HIV-infected persons (especially those who are seropositive for *Bartonella*) should be considered. The development of microbial resistance is a theoretical possibility during prolonged antimicrobial therapy.

More complete analyses of risk factors for infections due to *B. henselae* and *B. quintana* must be undertaken. The route by which cats become infected with *B. henselae* and the way in which this organism persists in and is subsequently transmitted by these animals should be established. The potential for the elimination of feline infections due to *B. henselae* by antibiotic treatment and for the prevention of reinfection must be studied. A feline vaccine designed to prevent *B. henselae* infection should be developed, with the interruption of transmission to HIV-infected pet owners as the ultimate goal. The possible role of arthropod vectors in the transmission of *B. henselae* and *B. quintana* needs to be clarified.

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